Remarks

The Office Action dated February 3, 2009 has been carefully reviewed and the following comments are made in response thereto. In view of the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Without prejudice or disclaimer and for the sole purpose of advancing prosecution, Applicants have amended claim 11 to incorporate the features of claim 12, canceled claim 12 as well as amended claims 13 and 14. No new matter has been added.

Applicants respectfully draw the Examiner's attention to U.S. Patent Application No. 11/666,229, which contains technically related subject matter, and the art cited therein. In that application, the Patent Office has issued a non-final Office Action, a response to which is currently outstanding.

The Rejections under 35 U.S.C. 112 should be withdrawn

Claims 11 to 15 and 24 to 38 were rejected for allegedly failing to comply with the written description requirement. Applicants respectfully disagree. For the sole purpose of advancing prosecution and without acquiescing to the merits, Applicants have amended claim 11 to incorporate the features of claim 12. As amended, claim 11 complies with the written description requirement (*see* pages 2 to 3 of the Office Action). Accordingly, this rejection is moot.

The Rejections under 35 U.S.C. 103(a) should be withdrawn

The pending claims were rejected for allegedly being obvious over Teichberg in view of Aminova *et al.* and Lu *et al.* Applicants respectfully disagree.

The pending claims are directed to (1) methods of promoting tissue neovascularization in a subject in need thereof with (2) compositions containing at least a 2-oxoacid in (3) an amount effective to induce HIF-1 mediated gene expression. Under a *Graham v. John Deere* analysis, the pending claims are clearly not obvious. None of the references cited or the skill in the art at the time of the invention discloses or suggests the combination of each claim element; accordingly the pending claims are not obvious.

The crux of the obviousness rejection is that since certain 2-oxoacids have been linked to reduce brain glutamate levels and since a reduction in glutamate levels has been implicated in HIF-1 mediated gene expression, the claims are obvious. The Office Action fails to provide any reasonable basis other

than inherency that the novel methods of the instant application are obvious. In particular, the Office Action fails to provide a reasonable basis for a link between HIF-1 mediated gene expression, administration of 2-oxoacids and tissue neovascularization.

Teichberg discloses methods of reducing extracellular brain glutamate levels by administration of a therapeutically effective amount of an agent capable of reducing blood glutamate levels (*see e.g.* ¶ [0020]). Teichberg discloses numerous of such agents including oxaloacetate diethylesters, glutamate modifying enzymes, lipoic acid, lipoic acid precusors, and inhibitors of glutamate synthesizing enzymes (*see e.g.* ¶¶ [0025], [0026], [0027], [0028], [0040], [0052], [0053]). As acknowledged in the Office Action, Teichberg fails to disclose the relationship between the glutamate concentration and HIF-1 mediated gene expression (*see* page 5). In addition, Teichberg fails to disclose or suggest the any relationship between glutamate concentration and tissue neovascularization (a required feature of the pending claims). Teichberg fails to disclose or suggest that the compounds administered to reduce glutamate levels can be administered to promote tissue vascularization or induce HIF-1 mediated gene expression. Teichberg also fails to disclose or suggest that administration of these compounds in an amount effective to induce HIF-1 mediated gene expression.

Aminova *et al.* discloses that HIF-1 levels are higher at reduced glutamate levels (*see* page 5 of the Office Action). Aminova *et al.* does not disclose or suggest any link between HIF-1 levels and neovascularization. Even if Aminova *et al.* were to disclose such a link, the Examiner cannot rely on the manuscript as anything other than merely providing further support for the Examiner's arguments. As the Examiner is aware, the Aminova *et al.* article published after the effective filing date of this application (*i.e.* after the filing date of the both the provisional and PCT application whose benefit this application claims). As such, Aminova *et al.* is not prior art.

Lu *et al.* teaches that pyruvate regulates hypoxia inducible gene expression independently of hypoxia by stimulating the accumulation of HIF-1α (*see* page 5 of the Office Action). Lu *et al.* does not disclose or suggest a link between HIF-1α gene expression and tissue neovascularization.

The combination of these references in view of the skill in the art at the time of the invention does not render the pending claims obvious. Clearly, the combination of the references does not disclose or suggest each and every element of the pending claims in particular a method promoting tissue neovascularization. The doctrine of inherency cannot be used to fill any gaping holes in the obviousness analysis (*see* M.P.E.P. 2143.03 (all claim limitations must be considered in an obviousness analysis)). As discussed above, Teichberg discloses a laundry list of agents that are effective to reduce extracellular

brain glutamate levels that encompasses hundreds if not thousands of different compounds, including NAD$^+$ (*see* ¶ [0025]). The mere disclosure of that laundry list of agents does not imply that all of these agents can be used by as alleged by the Examiner. For example, the instant application discloses that NAD+/NADH are not responsible for HIF-1α activation (*see* page 30, lines 13 to 15). Thus, administration of NAD+/NADH would not result in inducement of HIF-1 mediated gene expression and thus could not be used a method of promoting tissue neovascularization. Similarly, two other suitable agents disclosed by Teichberg are pyruvate and oxaloacetate (*see* ¶ [0025]). Teichberg discloses that pyruvate significantly increases plasma glutamate concentration while oxaloacetate significantly reduces plasma glutamate (*see* Example 2, ¶ [0191]). The crux of the obviousness rejection is that a reduction of glutamate results in an increase HIF-1 expression (*see* page 6 of Office Action). Accordingly, the combination of the references also provides no reasonable expectation of success since pyruvate and oxaloacetate were observed to have the opposite effects. These contradictory results point to the non-obviousness of the invention and are evidence of hindsight reasoning. Much like in *Takeda Chemicals Indus. v. Alapharma Pty. Ltd.*, rather than identifying a predictable solution for the problem (*e.g.* tissue neovascularization), the prior art discloses a broad selection of compounds any one of which could have been used for further investigation; accordingly, the claimed invention is also not obvious to try. *See* 492 F.3d 1350, 1359 (Fed. Cir. 2007).

Furthermore, at most Teichberg discloses a genus of compounds that reduce the level of extracellular glutamate. These compounds as discussed above include oxaloacetate diethylesters, glutamate modifying enzymes, lipoic acid, lipoic acid precusors, and inhibitors of glutamate synthesizing enzymes (*see e.g.* ¶¶ [0025], [0026], [0027], [0028], [0040], [0052], [0053]). Some species of that genus were identified by the Applicants as being able to promote tissue neovascularization. Other members of that genus are not able to promote tissue neovascularization. The fact that a claimed species is encompassed by the prior art is in itself insufficient to establish *prima facie* obviousness (M.P.E.P. 2144.08).

The reliance on the doctrine of inherency for the claim element "method of promoting tissue neovascularization" is misplaced (*see* page 6 of the Office Action). Under the doctrine of inherency, the discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, cannot impart patentability to claims to the known composition (*In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992)). The doctrine of inherency pertains to anticipation under 35 U.S.C. 102 and not obviousness under 35 U.S.C. 103 (*see Jones v. Hardy*, 727 F.2d 1524, 1529

(Fed. Cir. 1984) ("though anticipation is the epitome of obviousness, [they] are separate and distinct concepts")). The currently pending claims are directed to methods. Non-obvious methods of using compound to treat a disease, such as the claims in this application, are clearly patentable even when the compound was known (*see In re Schoenwald*, 964 F.3d at 1122; *In re Gleave*, 90 U.S.P.Q.2d 1235, 1241 (Fed. Cir. 2009) ("If the *use* Gleave discovered is new, he will be able to patent that method of use"); *see also* 35 U.S.C. 101 ("new and useful processes" are patentable)). Since the claimed methods are clearly novel, Applicants should be able to obtain a patent to that method of use. If the inherency argument asserted in the Office Action were to be true then there could be no patent directed to new uses of known compounds – i.e. new processes. In the absence of a disclosure in the prior art that suggests that the claimed method is obvious, the inherent properties of a composition cannot be relied upon for the invalidity of a method. Accordingly, for that reason alone, the obviousness rejection should be withdrawn.

While reliance on the doctrine of inherency is misplaced, even if the doctrine of inherency were applicable, the claims are nevertheless not obvious. Teichberg discloses a method of reducing glutamate levels (*see e.g.* claim 60) in a variety of diseases including patients undergoing coronary bypass surgery. Teichberg administers these agents because high glutamate levels are associated with neurogenerative diseases including stroke and because glutamate is associated with neuronal damage (*see* ¶¶ [0006], [0007]). Patients undergoing coronary bypass surgery are at an elevated risk of stroke. The combination of the references and the skill in the art does not disclose or suggest that HIF-1 mediated gene expression is linked to tissue neovascularization and that tissue neovascularization may be induced by certain 2-oxoacids. The combination of the references and the skill in the art does not disclose or suggest that administration of 2-oxacids would necessarily result in tissue neovascularization or that the amount of the agents administered is sufficient to induce HIF-1 mediated gene expression. Furthermore, as discussed, the agents disclosed by Teichberg are not necessarily effective in inducing HIF-1 mediated gene expression. Thus, contrary to the allegations in the Office Action, administration of an agent disclosed by Teichberg would not necessarily result in increased HIF-1 gene expression and accordingly would not necessarily result in tissue neovascularization. Accordingly, the claims are not obvious.

For the foregoing reasons, Applicants submit that the pending claims are not obvious and that the obviousness rejection be withdrawn.

Conclusion

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicants respectfully request a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,
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